

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A method of concurrent imaging in a mammal comprising:
 - a) administering to said mammal a vitronectin receptor targeted imaging agent and a perfusion imaging agent; and
 - b) concurrently detecting the vitronectin receptor targeted imaging agent bound at the vitronectin receptor and the perfusion imaging agent; and
 - c) forming an image from the detection of said vitronectin targeted imaging agent and said perfusion imaging agent; wherein said vitronectin targeted imaging agent comprises a peptide selected from the group consisting of:

cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val));

cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido));

cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido));

[[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};

cyclo{Arg-Gly-Asp-D-Nal-Lys([5-[carbonyl]-2-pyridinyl]diazenido));

[[5-[carbonyl]-2-pyridinyl]-diazenido]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal};

cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val);

N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-Phe))-O-cyclo(Lys-Arg-Gly-Asp-D-Phe);

N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp))-O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp);

cyclo(Arg-Gly-Asp-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido))-D-Val);

cyclo(N-Me-Arg-Gly-Asp-ATA-D-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido)));

cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val);

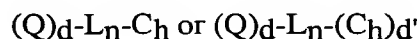
cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};

cyclo(Arg-Gly-Asp-D-Phe-Lys); and

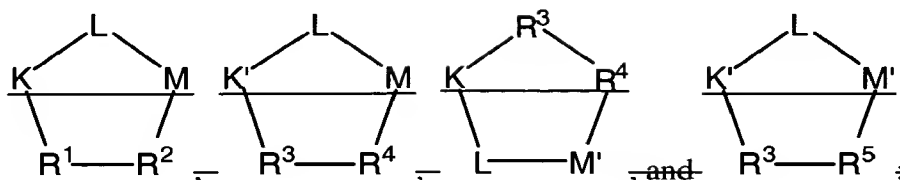
Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys)).

2. (original) The method of claim 1, wherein the vitronectin receptor is selected from the group: $\alpha_v\beta_3$, and $\alpha_v\beta_5$.
3. (original) The method according to claim 1, wherein the vitronectin receptor is $\alpha_v\beta_3$.
4. (original) The method of claim 1 wherein the perfusion imaging agent is selected from the group consisting of: an ultrasound perfusion agent, an MRI perfusion imaging agent, and a radiolabelled imaging agent.

5. (original) The method of claim 1 wherein the perfusion imaging agent is hexakis methoxyisobutyl isonitrile Technetium(I) (^{99m}Tc -Sestamibi), ^{210}Tl , ^{99m}Tc -tetrofosmin, ^{99m}Tc -furifosmin, or ^{99m}Tc -NOET.
6. (original) The method according to claim 1, wherein the vitronectin receptor targeted imaging agent is a diagnostic metallopharmaceutical.
7. (original) The method according to claim 6, wherein the vitronectin receptor targeting agent is a vitronectin antagonist.
8. (original) The method according to claim 6, wherein the vitronectin receptor targeting agent is a vitronectin agonist.
9. (original) The method of claim 6, wherein the diagnostic metallopharmaceutical comprises a metal and a compound, wherein the compound comprises:
- a) a chelator capable of chelating the metal;
 - b) a targeting moiety, wherein the targeting moiety is bound to the chelator; and
 - c) 0-1 linking groups between the targeting moiety and the chelator;
- wherein the targeting moiety is a peptide or peptidomimetic which binds to a vitronectin receptor.
10. (Currently amended) The method according to claim 9, wherein compound is of the formula:



wherein, Q is a peptide ~~independently selected from the group:~~



~~K is an L-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethyleysteine, δ -N-2-imidazolinylnornithine, δ -N-benzylcarbamoynornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;~~

~~K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethyleysteine, δ -N-2-imidazolinylnornithine, δ -N-benzylcarbamoynornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;~~

~~L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;~~

~~M is L-aspartic acid;~~

~~M' is D-aspartic acid;~~

~~R¹ is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;~~

~~R² is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;~~

~~R³ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;~~

~~R⁴ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;~~

~~R⁵ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine,~~

~~L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine,
L-methionine, and 2-aminothiazole-4-acetic acid;~~

~~provided that one of R¹, R², R³, R⁴, and R⁵ in each Q is substituted with a bond to L_n;~~

~~further provided that when R² is 2-aminothiazole-4-acetic acid, K is~~

~~N-methylarginine, further provided that when R⁴ is 2-aminothiazole-4-acetic acid, K~~

~~and K' are N-methylarginine, and still further provided that when R⁵ is~~

~~2-aminothiazole-4-acetic acid, K' is N-methylarginine;~~

~~d is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10~~ selected from the group consisting of:

cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val));

cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido)));

cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido)));

[[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe))-cyclo{Lys-Arg-Gly-Asp-D-Phe};

cyclo{Arg-Gly-Asp-D-Nal-Lys([[5-[carbonyl]-2-pyridinyl]diazenido))};

[[5-[carbonyl]-2-pyridinyl]-diazenido]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal))-cyclo{Lys-Arg-Gly-Asp-D-Nal};

cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val);

N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-Phe))-O-cyclo(Lys-Arg-Gly-Asp-D-Phe);

N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp))-O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp);

cyclo(Arg-Gly-Asp-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido))-D-Val);

cyclo(N-Me-Arg-Gly-Asp-ATA-D-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido)));

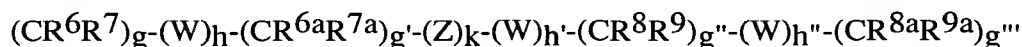
cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val);

cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};

cyclo(Arg-Gly-Asp-D-Phe-Lys); and

Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys)).

L_n is a linking group having the formula:



provided that $g+h+g'+k+h'+g''+h''+g'''$ is other than 0;

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, (OCH₂CH₂)_s, (CH₂CH₂O)_{s'}, (OCH₂CH₂CH₂)_{s''}, (CH₂CH₂CH₂O)_t, and (aa)_{t'};

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R¹⁰, C₃₋₁₀ cycloalkyl substituted with 0-3 R¹⁰, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁰;

R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹ and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO₃H, PO₃H, C₁₋₅ alkyl substituted with 0-3 R¹⁰, aryl substituted with 0-3 R¹⁰, benzyl substituted with 0-3 R¹⁰, and C₁₋₅ alkoxy substituted with 0-3 R¹⁰, NHC(=O)R¹¹, C(=O)NHR¹¹, NHC(=O)NHR¹¹, NHR¹¹, R¹¹, and a bond to C_H;

R¹⁰ is independently selected at each occurrence from the group: a bond to C_H, COOR¹¹, OH, NHR¹¹, SO₃H, PO₃H, aryl substituted with 0-3 R¹¹, C₁₋₅ alkyl substituted with 0-1 R¹², C₁₋₅ alkoxy substituted with 0-1 R¹², and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹¹;

R¹¹ is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R¹², a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹², C₃₋₁₀ cycloalkyl substituted with 0-1 R¹², polyalkylene glycol substituted with 0-1 R¹², carbohydrate substituted with 0-1 R¹², cyclodextrin substituted with 0-1 R¹², amino acid substituted with 0-1 R¹², polycarboxyalkyl substituted with 0-1 R¹², polyazaalkyl substituted with 0-1 R¹², peptide substituted with 0-1 R¹², wherein the peptide is comprised of 2-10 amino acids, and a bond to C_H;

R^{12} is a bond to C_h ;

k is selected from 0, 1, and 2;

h is selected from 0, 1, and 2;

h' is selected from 0, 1, 2, 3, 4, and 5;

h'' is selected from 0, 1, 2, 3, 4, and 5;

g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

g'' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

g''' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

s is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

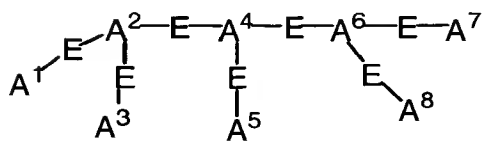
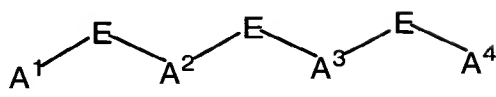
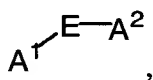
s' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

s'' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

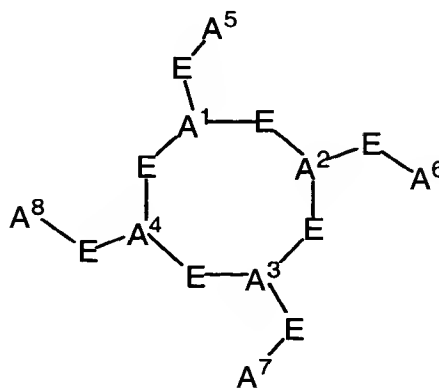
t is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

C_h is a metal bonding unit having a formula selected from the group:



, and



;

A¹, A², A³, A⁴, A⁵, A⁶, A⁷, and A⁸ are independently selected at each occurrence from the group N, NR¹³, NR¹³R¹⁴, S, SH, O, OH, PR¹³, PR¹³R¹⁴, P(O)R¹⁵R¹⁶, and a bond to L_n;

E is a bond, CH, or a spacer group independently selected at each occurrence from the group:

C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, aryl substituted with 0-3 R¹⁷, C₃-₁₀ cycloalkyl substituted with 0-3 R¹⁷, heterocyclo-C₁-₁₀ alkyl substituted with 0-3 R¹⁷, wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C₆-₁₀ aryl-C₁-₁₀ alkyl substituted with 0-3 R¹⁷, C₁-₁₀ alkyl-C₆-₁₀ aryl- substituted with 0-3 R¹⁷, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁷;

R¹³, and R¹⁴ are each independently selected from the group: a bond to L_n, hydrogen, C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, aryl substituted with 0-3 R¹⁷, C₁-₁₀ cycloalkyl substituted with 0-3 R¹⁷, heterocyclo-C₁-₁₀ alkyl substituted with 0-3 R¹⁷, wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C₆-₁₀ aryl-C₁-₁₀ alkyl substituted with 0-3 R¹⁷, C₁-₁₀ alkyl-C₆-₁₀ aryl- substituted with 0-3 R¹⁷, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁷, and an electron, provided that when one of R¹³ or R¹⁴ is an electron, then the other is also an electron;

alternatively, R¹³ and R¹⁴ combine to form =C(R²⁰)(R²¹);

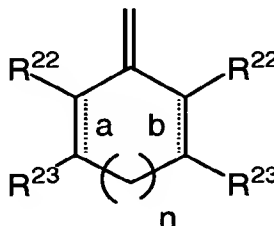
R¹⁵ and R¹⁶ are each independently selected from the group: a bond to L_n, -OH, C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, aryl substituted with 0-3 R¹⁷, C₃-C₁₀ cycloalkyl substituted with 0-3 R¹⁷, heterocyclo-C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C₆-C₁₀ aryl-C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, C₁-C₁₀ alkyl-C₆-C₁₀ aryl- substituted with 0-3 R¹⁷, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁷;

R¹⁷ is independently selected at each occurrence from the group: a bond to L_n, =O, F, Cl, Br, I, -CF₃, -CN, -CO₂R¹⁸, -C(=O)R¹⁸, -C(=O)N(R¹⁸)₂, -CHO, -CH₂OR¹⁸, -OC(=O)R¹⁸, -OC(=O)OR^{18a}, -OR¹⁸, -OC(=O)N(R¹⁸)₂, -NR¹⁹C(=O)R¹⁸, -NR¹⁹C(=O)OR^{18a}, -NR¹⁹C(=O)N(R¹⁸)₂, -NR¹⁹SO₂N(R¹⁸)₂, -NR¹⁹SO₂R^{18a}, -SO₃H, -SO₂R^{18a}, -SR¹⁸, -S(=O)R^{18a}, -SO₂N(R¹⁸)₂, -N(R¹⁸)₂, -NHC(=S)NHR¹⁸, =NOR¹⁸, NO₂, -C(=O)NHOR¹⁸, -C(=O)NHN(R¹⁸)R^{18a}, -OCH₂CO₂H, 2-(1-morpholino)ethoxy, C₁-C₅ alkyl, C₂-C₄ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylmethyl, C₂-C₆ alkoxyalkyl, aryl substituted with 0-2 R¹⁸, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

R¹⁸, R^{18a}, and R¹⁹ are independently selected at each occurrence from the group: a bond to L_n, H, C₁-C₆ alkyl, phenyl, benzyl, C₁-C₆ alkoxy, halide, nitro, cyano, and trifluoromethyl;

R²⁰ and R²¹ are independently selected from the group: H, C₁-C₁₀ alkyl, -CN, -CO₂R²⁵, -C(=O)R²⁵, -C(=O)N(R²⁵)₂, C₂-C₁₀ 1-alkene substituted with 0-3 R²³, C₂-C₁₀ 1-alkyne substituted with 0-3 R²³, aryl substituted with 0-3 R²³, unsaturated 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R²³, and unsaturated C₃-10 carbocycle substituted with 0-3 R²³;

alternatively, R²⁰ and R²¹, taken together with the divalent carbon radical to which they are attached form:



R²² and R²³ are independently selected from the group: H, R²⁴, C₁-C₁₀ alkyl substituted with 0-3 R²⁴, C₂-C₁₀ alkenyl substituted with 0-3 R²⁴, C₂-C₁₀ alkynyl substituted with 0-3 R²⁴, aryl substituted with 0-3 R²⁴, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R²⁴, and C₃-10 carbocycle substituted with 0-3 R²⁴;

alternatively, R²², R²³ taken together form a fused aromatic or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

a and b indicate the positions of optional double bonds and n is 0 or 1;

R²⁴ is independently selected at each occurrence from the group: =O, F, Cl, Br, I, -CF₃,
-CN, -CO₂R²⁵, -C(=O)R²⁵, -C(=O)N(R²⁵)₂, -N(R²⁵)₃⁺, -CH₂OR²⁵, -OC(=O)R²⁵,
-OC(=O)OR^{25a}, -OR²⁵, -OC(=O)N(R²⁵)₂, -NR²⁶C(=O)R²⁵, -NR²⁶C(=O)OR^{25a},
-NR²⁶C(=O)N(R²⁵)₂, -NR²⁶SO₂N(R²⁵)₂, -NR²⁶SO₂R^{25a}, -SO₃H, -SO₂R^{25a},
-SR²⁵, -S(=O)R^{25a}, -SO₂N(R²⁵)₂, -N(R²⁵)₂, =NOR²⁵, -C(=O)NHOR²⁵,
-OCH₂CO₂H, and 2-(1-morpholino)ethoxy; and,

R²⁵, R^{25a}, and R²⁶ are each independently selected at each occurrence from the group:
hydrogen and C₁-C₆ alkyl;

and a pharmaceutically acceptable salt thereof.

11. (Currently amended) The method according to claim 10 wherein

~~L is glycine;~~

~~R¹ is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: L valine, D valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, tyrosine, phenylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, lysine, ornithine, 1,2-diaminobutyric acid, and 1,2-diaminopropionic acid;~~

~~R² is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, tyrosine, L phenylalanine, D phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, and 2-aminothiazole-4-acetic acid;~~

~~R³ is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: D valine, D alanine, D leucine, D isoleucine, D norleucine, D 2-aminobutyric acid, D tyrosine, D phenylalanine, D phenylglycine,~~

~~D-cyclohexylalanine, D-homophenylalanine, D-lysine, D-serine, D-ornithine,
D-1,2-diaminobutyric acid, and D-1,2-diaminopropionic acid;~~

~~R⁴ is an amino acid, optionally substituted with a bond to L_n, independently selected at each
occurrence from the group: D-valine, D-alanine, D-leucine, D-isoleucine,
D-norleucine, D-2-aminobutyric acid, D-tyrosine, D-phenylalanine, D-thienylalanine,
D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine,
D-lysine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, and
2-aminothiazole-4-acetic acid;~~

~~R⁵ is an amino acid, optionally substituted with a bond to L_n, independently selected at each
occurrence from the group: L-valine, L-alanine, L-leucine, L-isoleucine,
L-norleucine, L-2-aminobutyric acid, L-tyrosine, L-phenylalanine, L-thienylalanine,
L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine,
L-lysine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, and
2-aminothiazole-4-acetic acid;~~

~~d is selected from 1, 2, and 3;~~

W is independently selected at each occurrence from the group: O, NH, NHC(=O),
C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂,
(OCH₂CH₂)_s, (CH₂CH₂O)_s', (OCH₂CH₂CH₂)_s", and (CH₂CH₂CH₂O)_t,

Z is selected from the group: aryl substituted with 0-1 R¹⁰, C₃₋₁₀ cycloalkyl substituted
with 0-1 R¹⁰, and a 5-10 membered heterocyclic ring system containing 1-4
heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹⁰;
R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹, and R^{9a} are independently selected at each occurrence from
the group: H, =O, COOH, SO₃H, C₁₋₅ alkyl substituted with 0-1 R¹⁰, aryl
substituted with 0-1 R¹⁰, benzyl substituted with 0-1 R¹⁰, and C₁₋₅ alkoxy
substituted with 0-1 R¹⁰, NHC(=O)R¹¹, C(=O)NHR¹¹, NHC(=O)NHR¹¹, NHR¹¹,
R¹¹, and a bond to C_H;

R^{10} is independently selected at each occurrence from the group: $COOR^{11}$, OH, NHR^{11} , SO_3H , aryl substituted with 0-1 R^{11} , a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{11} , C_1 - C_5 alkyl substituted with 0-1 R^{12} , C_1 - C_5 alkoxy substituted with 0-1 R^{12} , and a bond to C_h ;

R^{11} is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R^{12} , a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{12} , polyalkylene glycol substituted with 0-1 R^{12} , carbohydrate substituted with 0-1 R^{12} , cyclodextrin substituted with 0-1 R^{12} , amino acid substituted with 0-1 R^{12} , and a bond to C_h ;

k is 0 or 1;

h is 0 or 1;

h' is 0 or 1;

s is selected from 0, 1, 2, 3, 4, and 5;

s' is selected from 0, 1, 2, 3, 4, and 5;

s" is selected from 0, 1, 2, 3, 4, and 5;

t is selected from 0, 1, 2, 3, 4, and 5;

A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , A^7 , and A^8 are independently selected at each occurrence from the group: NR^{13} , $NR^{13}R^{14}$, S, SH, OH, and a bond to L_n ;

E is a bond, CH, or a spacer group independently selected at each occurrence from the group: C_1 - C_{10} alkyl substituted with 0-3 R^{17} , aryl substituted with 0-3 R^{17} , C_3 -10 cycloalkyl substituted with 0-3 R^{17} , and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17} ;

R¹³, and R¹⁴ are each independently selected from the group: a bond to L_n, hydrogen, C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, aryl substituted with 0-3 R¹⁷, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁷, and an electron, provided that when one of R¹³ or R¹⁴ is an electron, then the other is also an electron;

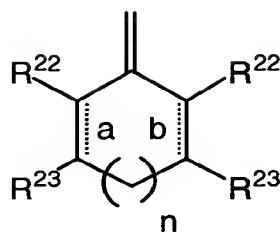
alternatively, R¹³ and R¹⁴ combine to form =C(R²⁰)(R²¹);

R¹⁷ is independently selected at each occurrence from the group: a bond to L_n, =O, F, Cl, Br, I, -CF₃, -CN, -CO₂R¹⁸, -C(=O)R¹⁸, -C(=O)N(R¹⁸)₂, -CH₂OR¹⁸, -OC(=O)R¹⁸, -OC(=O)OR^{18a}, -OR¹⁸, -OC(=O)N(R¹⁸)₂, -NR¹⁹C(=O)R¹⁸, -NR¹⁹C(=O)OR^{18a}, -NR¹⁹C(=O)N(R¹⁸)₂, -NR¹⁹SO₂N(R¹⁸)₂, -NR¹⁹SO₂R^{18a}, -SO₃H, -SO₂R^{18a}, -S(=O)R^{18a}, -SO₂N(R¹⁸)₂, -N(R¹⁸)₂, -NHC(=S)NHR¹⁸, =NOR¹⁸, -C(=O)NHN(R¹⁸)₂, -OCH₂CO₂H, and 2-(1-morpholino)ethoxy;

R¹⁸, R^{18a}, and R¹⁹ are independently selected at each occurrence from the group: a bond to L_n, H, and C₁-C₆ alkyl;

R²⁰ and R²¹ are independently selected from the group: H, C₁-C₅ alkyl, -CO₂R²⁵, C₂-C₅ 1-alkene substituted with 0-3 R²³, C₂-C₅ 1-alkyne substituted with 0-3 R²³, aryl substituted with 0-3 R²³, and unsaturated 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R²³;

alternatively, R²⁰ and R²¹, taken together with the divalent carbon radical to which they are attached form:



R^{22} and R^{23} are independently selected from the group: H, and R^{24} ;

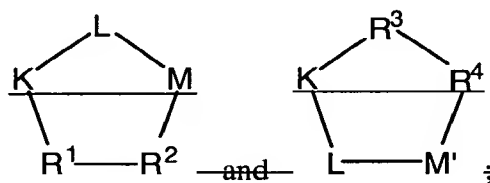
alternatively, R^{22} , R^{23} taken together form a fused aromatic or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

R^{24} is independently selected at each occurrence from the group: $-\text{CO}_2R^{25}$, $-\text{C}(=\text{O})\text{N}(R^{25})_2$, $-\text{CH}_2\text{OR}^{25}$, $-\text{OC}(=\text{O})R^{25}$, $-\text{OR}^{25}$, $-\text{SO}_3\text{H}$, $-\text{N}(R^{25})_2$, and $-\text{OCH}_2\text{CO}_2\text{H}$; and,

R^{25} is independently selected at each occurrence from the group: H and $\text{C}_1\text{-C}_3$ alkyl.

12. (Currently amended) The method according to claim 10 wherein

~~Q is a peptide selected from the group:~~



~~R^1 is L-valine, D-valine, D-lysine optionally substituted on the ϵ amino group with a bond to L_n or L-lysine optionally substituted on the ϵ amino group with a bond to L_n ;~~

~~R² is L-phenylalanine, D-phenylalanine, D-1-naphthylalanine, 2-aminothiazole-4-acetic acid,
L-lysine optionally substituted on the ε-amino group with a bond to L_n, or tyrosine, the
tyrosine optionally substituted on the hydroxy group with a bond to L_n;~~

~~R³ is D-valine, D-phenylalanine, or L-lysine optionally substituted on the ε-amino group with
a bond to L_n;~~

~~R⁴ is D-phenylalanine, D-tyrosine substituted on the hydroxy group with a bond to L_n, or
L-lysine optionally substituted on the ε-amino group with a bond to L_n;~~

~~provided that one of R¹ and R² in each Q is substituted with a bond to L_n, and further
provided that when R² is 2-aminothiazole-4-acetic acid, K is N-methylarginine;~~

~~d is 1 or 2;~~

W is independently selected at each occurrence from the group: NHC(=O), C(=O)NH,
C(=O), (CH₂CH₂O)_{s'}, and (CH₂CH₂CH₂O)_t;

R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹, and R^{9a} are independently selected at each occurrence from
the group: H, NHC(=O)R¹¹, and a bond to C_h;

k is 0;

h" is selected from 0, 1, 2, and 3;

g is selected from 0, 1, 2, 3, 4, and 5;

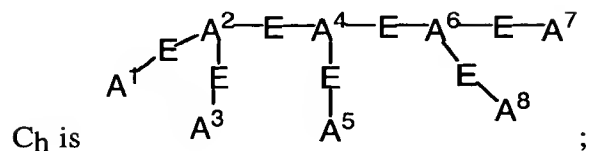
g' is selected from 0, 1, 2, 3, 4, and 5;

g" is selected from 0, 1, 2, 3, 4, and 5;

g''' is selected from 0, 1, 2, 3, 4, and 5;

s' is 1 or 2;

t is 1 or 2;



A¹ is selected from the group: OH, and a bond to L_n;

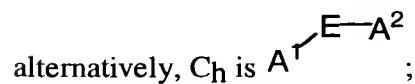
A², A⁴, and A⁶ are each N;

A³, A⁵, and A⁸ are each OH;

A⁷ is a bond to L_n or NH-bond to L_n;

E is a C₂ alkyl substituted with 0-1 R¹⁷;

R¹⁷ is =O;



A¹ is NH₂ or N=C(R²⁰)(R²¹);

E is a bond;

A² is NHR¹³;

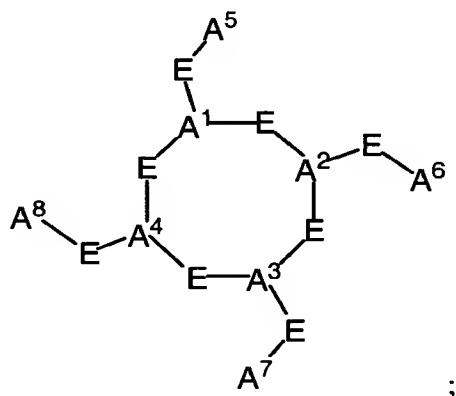
R¹³ is a heterocycle substituted with R¹⁷, the heterocycle being selected from pyridine and pyrimidine;

R¹⁷ is selected from a bond to L_n, C(=O)NHR¹⁸, and C(=O)R¹⁸;

R¹⁸ is a bond to L_n;

R²⁴ is selected from the group: -CO₂R²⁵, -OR²⁵, -SO₃H, and -N(R²⁵)₂;

R²⁵ is independently selected at each occurrence from the group: hydrogen and methyl;



alternatively, C_H is

A¹, A², A³, and A⁴ are each N;

A⁵, A⁶, and A⁸ are each OH;

A⁷ is a bond to L_n;

E is a C₂ alkyl substituted with 0-1 R¹⁷; and,

R¹⁷ is =O.

13. (original) The method of claim 6 wherein the diagnostic metallopharmaceutical comprises a radioisotope.

14. (original) The method of claim 13 wherein the radioisotope is selected from the group consisting of ^{99m}Tc, ⁹⁵Tc, ¹¹¹In, ⁶²Cu, ⁶⁴Cu, ⁶⁷Ga, and ⁶⁸Ga.

15. (original) The method of claim 14 wherein the radioisotope is selected from the group consisting of In-111, and Tc-99m.

16. (original) The method of claim 9, wherein the metallopharmaceutical is a diagnostic radiopharmaceutical and the metal is a radioisotope selected from the group: ^{99m}Tc, ⁹⁵Tc, ¹¹¹In, ⁶²Cu, ⁶⁴Cu, ⁶⁷Ga, and ⁶⁸Ga.

17. (original) The method of claim 16 wherein the radioisotope is selected from the group consisting of ¹¹¹In, and ^{99m}Tc.

18. (original) The method according to claim 16, wherein the radioisotope is ^{99m}Tc or ⁹⁵Tc, the radiopharmaceutical further comprises a first ancillary ligand and a second ancillary ligand capable of stabilizing the radiopharmaceutical.

19. (original) The method according to claim 16, wherein the radioisotope is ^{99m}Tc.

20. (currently amended) The method according to claim 19, wherein the radiopharmaceutical is selected from the group:

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val)) ~~SEQ ID NO: 4;~~

DOCKET NO.: BMS-2201 (PH-7201)
Application No.: 09/995,388
Office Action Dated: June 15, 2005

PATENT
REPLY FILED UNDER EXPEDITED
PROCEDURE PURSUANT TO
37 CFR § 1.116

~~^{99m}Tc(tricine)(TPPMS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly)) SEQ ID NO: 2;~~

~~^{99m}Tc(tricine)(TPPDS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly)) SEQ ID NO: 2;~~

~~^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly)) SEQ ID NO: 2;~~

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido]])) SEQ ID NO: 3;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido]])) SEQ ID NO: 4;

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe}))-cyclo{Lys-Arg-Gly-Asp-D-Phe}) SEQ ID NO: 5;

^{99m}Tc(tricine)(TPPTS)(cyclo{ Arg-Gly-Asp-D-Nal-Lys([5-[carbonyl]-2-pyridinyl]diazenido])) SEQ ID NO: 6;

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]-diazenido]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal}))-cyclo{Lys-Arg-Gly-Asp-D-Nal}) SEQ ID NO: 7;

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val)) SEQ ID NO: 1;

^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-Phe)))-O-cyclo(Lys-Arg-Gly-Asp-D-Phe)) SEQ ID NO: 8;

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})(\text{N}-[[5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}]\text{-Glu}(\text{O-cyclo}(\text{D-Tyr}(3\text{-aminopropyl})\text{-Val-Arg-Gly-Asp}))- \text{O-cyclo}(\text{D-Tyr}(3\text{-aminopropyl})\text{-Val-Arg-Gly-Asp}))$ ~~SEQ ID NO: 9;~~

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})(\text{cyclo}(\text{Arg-Gly-Asp-Lys}(\text{N}-[[5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}]))\text{-D-Val}))$ ~~SEQ ID NO: 10;~~

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})(\text{cyclo}(\text{D-Lys}([5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}))\text{-D-Phe-D-Asp-Gly-Arg}))$ ~~SEQ ID NO: 11;~~

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})([5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}\text{-Glu}(\text{cyclo}(\text{D-Lys-D-Phe-D-Asp-Gly-Arg}))\text{-cyclo}(\text{D-Lys-D-Phe-D-Asp-Gly-Arg}))$ ~~SEQ ID NO: 12;~~

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})(\text{cyclo}(\text{D-Phe-D-Lys}([5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}))\text{-D-Asp-Gly-Arg}))$ ~~SEQ ID NO: 13;~~

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})(\text{cyclo}(\text{N-Me-Arg-Gly-Asp-ATA-D-Lys}(\text{N}-[[5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}]))))$ ~~SEQ ID NO: 14;~~

$^{99m}\text{Tc}(\text{tricine})(\text{TPPTS})(\text{cyclo}(\text{Cit-Gly-Asp-D-Phe-Lys}([5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}))))$ ~~SEQ ID NO: 15;~~ and

$^{99m}\text{Tc}(\text{tricine})(1,2,4\text{-triazole})(\text{cyclo}(\text{Arg-Gly-Asp-D-Tyr}(\text{N}-[[5\text{-[carbonyl]}-2\text{-pyridinyl]diazenido}]\text{-3-aminopropyl})\text{-Val}))$ ~~SEQ ID NO: 1.~~

21. (original) The method according to claim 16, wherein the radioisotope is ^{111}In .
22. (Currently amended) The method according to claim 21, wherein the radiopharmaceutical is selected from the group:

(DOTA-¹¹¹In)-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe} ~~SEQ ID NO: 8~~;
~~ID NO: 8~~;

cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-¹¹¹In)) ~~SEQ ID NO: 3~~; and,

cyclo(Arg-Gly-Asp-D-Phe-Lys)₂(DTPA-¹¹¹In) ~~SEQ ID NO: 3~~.

23. (original) The method according to claim 6 wherein the diagnostic metallopharmaceutical is comprised of a paramagnetic metal.

24. (original) The method according to claim 23 wherein the paramagnetic metal is selected from the group consisting of Gd(III), Dy(III), Fe(III) and Mn(II).

25. (original) The method according to claim 23 wherein the paramagnetic metal is Gd(III).

26. (original) The method according to claim 9, wherein the metal is a paramagnetic metal ion selected from the group Gd(III), Dy(III), Fe(III) and Mn(II).

27. (original) The method according to claim 26, wherein the metal ion is Gd(III).

28. (Currently amended) The method according to claim 27, wherein the contrast agent is:

cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(Gd(III))-3-aminopropyl)-Val) ~~SEQ ID NO: 1~~.

29. (original) The method according to claim 6 wherein the diagnostic metallopharmaceutical is a X-ray contrast agent.

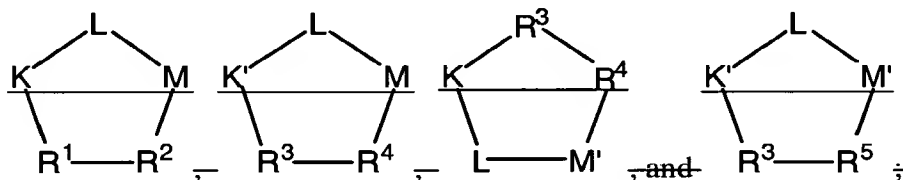
30. (original) The method according to claim 29 wherein the X-ray contrast agent comprises a vitronectin targeting agent; and the metal is selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir.
31. (original) The method according to claim 9, wherein diagnostic metallopharmaceutical is a X-ray contrast agent; the metal is selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir.
32. (original) A kit comprising a compound of claim 9 and a perfusion imaging agent.
33. (original) The kit of Claim 32 further comprising a reducing agent.
34. (original) The kit of Claim 33 wherein the reducing agent is tin(II).
35. (original) The kit of Claim 33 further comprising one or more ancillary ligands.
36. (original) The kit of Claim 35 wherein the ancillary ligands are tricine and TPPTS.
37. (original) A kit comprising a compound of claim 10 and a perfusion imaging agent.
38. (original) A method according to claim 1, wherein the vitronectin targeted imaging agent is a vitronectin targeted ultrasound imaging agent.
39. (original) A method according to Claim 38, wherein the ultrasound imaging agent comprises an echogenic gas or temperature activated gaseous precursor, and a compound, wherein the compound comprises:
- a) a surfactant;
 - b) a targeting moiety, wherein the targeting moiety is bound to the surfactant; and
 - c) 0-1 linking groups between the targeting moiety and surfactant;

wherein the targeting moiety is a peptide or peptidomimetic, which binds to a vitronectin receptor.

40. (Currently amended) A method according to Claim 39, wherein the compound is of the formula:



wherein, Q is a cyclic pentapeptide ~~independently selected from the group:~~



~~K is an L-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethyleysteine, δ -N-2-imidazolinylnornithine, δ -N-benzylcarbamoynornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;~~

~~K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethyleysteine, δ -N-2-imidazolinylnornithine, δ -N-benzylcarbamoynornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;~~

~~L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;~~

~~M is L-aspartic acid;~~

~~M' is D-aspartic acid;~~

~~R¹ is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;~~

~~R² is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;~~

~~R³ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;~~

~~R⁴ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine,~~

~~D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine,
D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;~~

~~R⁵ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each
occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine,
L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine,
L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine,
L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine,
L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine,
L-methionine, and 2-aminothiazole-4-acetic acid;~~

~~provided that one of R¹, R², R³, R⁴, and R⁵ in each Q is substituted with a bond to L_n;
further provided that when R² is 2-aminothiazole-4-acetic acid, K is
N-methylarginine, further provided that when R⁴ is 2-aminothiazole-4-acetic acid, K
and K' are N-methylarginine, and still further provided that when R⁵ is
2-aminothiazole-4-acetic acid, K' is N-methylarginine;~~

~~d is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 selected from the group consisting of:~~

~~cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-
aminopropyl)-Val));~~

~~cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido));~~

~~cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido));~~

~~[[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-
Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};~~

~~cyclo{Arg-Gly-Asp-D-Nal-Lys([5-[carbonyl]-2-pyridinyl]diazenido));~~

[[5-[carbonyl]-2-pyridinyl]-diazenido]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-
cyclo{Lys-Arg-Gly-Asp-D-Nal}};

cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-
amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val);

N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-
Phe))-O-cyclo(Lys-Arg-Gly-Asp-D-Phe);

N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(D-Tyr(3-aminopropyl)-
Val-Arg-Gly-Asp))-O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp);

cyclo(Arg-Gly-Asp-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido))-D-Val);

cyclo(N-Me-Arg-Gly-Asp-ATA-D-Lys(N-[[5-[carbonyl]-2-
pyridinyl]diazenido)));

cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-
aminopropyl)-Val);

cyclo{Lys-Arg-Gly-Asp-D-Phe}-cyclo{Lys-Arg-Gly-Asp-D-Phe};

cyclo(Arg-Gly-Asp-D-Phe-Lys); and

Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys));

Sf is a surfactant which is a lipid or a compound of the formula: $A^9-E^1-A^{10}$;

A⁹ is selected from the group: OH and OR²⁷;

A¹⁰ is OR²⁷;

R²⁷ is C(=O)C₁₋₂₀ alkyl;

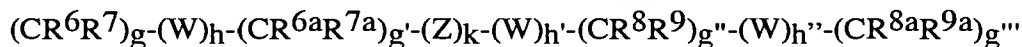
E¹ is C₁₋₁₀ alkylene substituted with 1-3 R²⁸;

R²⁸ is independently selected at each occurrence from the group: R³⁰, -PO₃H-R³⁰, =O, -CO₂R²⁹, -C(=O)R²⁹, -C(=O)N(R²⁹)₂, -CH₂OR²⁹, -OR²⁹, -N(R²⁹)₂, C₁-C₅ alkyl, and C₂-C₄ alkenyl;

R²⁹ is independently selected at each occurrence from the group: R³⁰, H, C₁-C₆ alkyl, phenyl, benzyl, and trifluoromethyl;

R³⁰ is a bond to L_n;

L_n is a linking group having the formula:



W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, (OCH₂CH₂)₂₀₋₂₀₀, (CH₂CH₂O)₂₀₋₂₀₀, (OCH₂CH₂CH₂)₂₀₋₂₀₀, (CH₂CH₂CH₂O)₂₀₋₂₀₀, and (aa)_t;

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R¹⁰, C₃₋₁₀ cycloalkyl substituted with 0-3 R¹⁰, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁰;

R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹ and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO₃H, PO₃H, C₁₋₅ alkyl substituted with 0-3 R¹⁰, aryl substituted with 0-3 R¹⁰, benzyl substituted with 0-3 R¹⁰, and C₁₋₅ alkoxy substituted with 0-3 R¹⁰, NHC(=O)R¹¹, C(=O)NHR¹¹, NHC(=O)NHR¹¹, NHR¹¹, R¹¹, and a bond to S_f;

R¹⁰ is independently selected at each occurrence from the group: a bond to S_f, COOR¹¹, OH, NHR¹¹, SO₃H, PO₃H, aryl substituted with 0-3 R¹¹, C₁₋₅ alkyl substituted with 0-1 R¹², C₁₋₅ alkoxy substituted with 0-1 R¹², and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹¹;

R¹¹ is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R¹², a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹², C₃₋₁₀ cycloalkyl substituted with 0-1 R¹², amino acid substituted with 0-1 R¹², and a bond to S_f;

R¹² is a bond to S_f;

k is selected from 0, 1, and 2;

h is selected from 0, 1, and 2;

h' is selected from 0, 1, 2, 3, 4, and 5;

h'' is selected from 0, 1, 2, 3, 4, and 5;

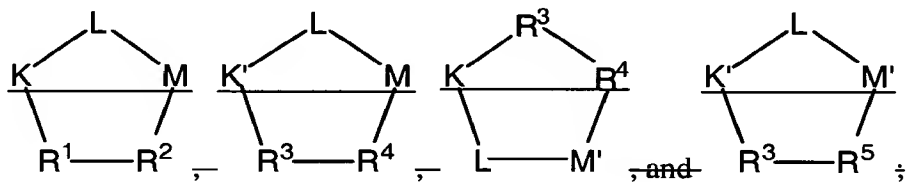
g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
 g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
 g'' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
 g''' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
 t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

and a pharmaceutically acceptable salt thereof.

41. (Currently amended) A method according to Claim 40, wherein ~~the compound is of the formula:~~



~~wherein, Q is a cyclic pentapeptide independently selected from the group:~~



~~N-methylarginine, lysine, homolysine, 2-aminoethyleysteine, δ -N-2-imidazolinylnornithine, δ -N-benzylcarbamoylornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;~~

~~K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethyleysteine, δ -N-2-imidazolinylnornithine, δ -N-benzylcarbamoylornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;~~

~~L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;~~

~~M is L-aspartic acid;~~

~~M' is D-aspartic acid;~~

~~R¹ is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;~~

~~R² is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;~~

~~R³ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;~~

~~R⁴ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;~~

~~R⁵ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine, L-methionine, and 2-aminothiazole-4-acetic acid;~~

~~provided that one of R¹, R², R³, R⁴, and R⁵ in each Q is substituted with a bond to L_n;
further provided that when R² is 2-aminothiazole-4-acetic acid, K is
N-methylarginine, further provided that when R⁴ is 2-aminothiazole-4-acetic acid, K
and K' are N-methylarginine, and still further provided that when R⁵ is
2-aminothiazole-4-acetic acid, K' is N-methylarginine;~~

S_f is a surfactant which is a lipid or a compound of the formula: $A^9-E^1-A^{10}$;

A⁹ is OR²⁷;

A¹⁰ is OR²⁷;

R²⁷ is C(=O)C₁₋₁₅ alkyl;

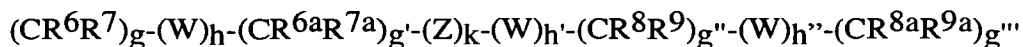
E¹ is C₁₋₄ alkylene substituted with 1-3 R²⁸;

R²⁸ is independently selected at each occurrence from the group: R³⁰, -PO₃H-R³⁰, =O, -CO₂R²⁹, -C(=O)R²⁹, -CH₂OR²⁹, -OR²⁹, and C₁-C₅ alkyl;

R²⁹ is independently selected at each occurrence from the group: R³⁰, H, C₁-C₆ alkyl, phenyl, and benzyl;

R³⁰ is a bond to L_n;

L_n is a linking group having the formula:



W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, (OCH₂CH₂)₂₀₋₂₀₀, (CH₂CH₂O)₂₀₋₂₀₀, (OCH₂CH₂CH₂)₂₀₋₂₀₀, (CH₂CH₂CH₂O)₂₀₋₂₀₀, and (aa)_{t'};

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R¹⁰, C₃₋₁₀ cycloalkyl substituted with 0-3 R¹⁰, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁰;

R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹ and R^{9a} are independently selected at each occurrence from the group: H, =O, C₁-C₅ alkyl substituted with 0-3 R¹⁰, and C₁-C₅ alkoxy substituted with 0-3 R¹⁰, and a bond to S_f;

R¹⁰ is independently selected at each occurrence from the group: a bond to S_f, COOR¹¹, OH, NHR¹¹, C₁₋₅ alkyl substituted with 0-1 R¹², and C₁₋₅ alkoxy substituted with 0-1 R¹²;

R¹¹ is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R¹², C₃₋₁₀ cycloalkyl substituted with 0-1 R¹², amino acid substituted with 0-1 R¹², and a bond to S_f;

R¹² is a bond to S_f;

k is selected from 0, 1, and 2;

h is selected from 0, 1, and 2;

h' is selected from 0, 1, 2, 3, 4, and 5;

h'' is selected from 0, 1, 2, 3, 4, and 5;

g is selected from 0, 1, 2, 3, 4, and 5;

g' is selected from 0, 1, 2, 3, 4, and 5;

g'' is selected from 0, 1, 2, 3, 4, and 5;

g''' is selected from 0, 1, 2, 3, 4, and 5;

s is selected from 0, 1, 2, 3, 4, and 5;

s' is selected from 0, 1, 2, 3, 4, and 5;

s'' is selected from 0, 1, 2, 3, 4, and 5;

t is selected from 0, 1, 2, 3, 4, and 5;

t' is selected from 0, 1, 2, 3, 4, and 5;

and a pharmaceutically acceptable salt thereof.

42. (Currently amended) A method according according to Claim 39, wherein the compound is selected from the group:

1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-(cyclo(Arg-Gly-Asp-D-Phe-Lys))-dodecane-1,12-dione ~~SEQ ID NO: 3~~;

1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG₃₄₀₀-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys))-dodecane-1,12-dione ~~SEQ ID NO: 3~~; and,

1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG₃₄₀₀-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))₂)-Dodecane-1,12-dione ~~SEQ ID NO: 16~~.

43. (original) The method according to claim 39, which further comprises a parenterally acceptable and an echogenic gas.

44. (original) The method according to claim 39, further comprising: 1,2-dipalmitoyl-sn-glycero-3-phosphotidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine.

45. (original) The method according to claim 43, wherein, the echogenic gas is a C₂₋₅ perfluorocarbon.

46. (original) A kit comprising a compound of Claim 39 and a perfusion imaging agent.

47. (original) The method according to claim 1, wherein the vitronectin targeted imaging agent and a perfusion imaging agent have spectrally separable gamma-emission energies.

48. (original) The method according to claim 1, wherein the images are displayed side-by-side to facilitate interpretation of the localization of the vitronectin targeted imaging in the body, relative to the distribution of the perfusion agent in the body.

49. (original) The method according to claim 1, wherein the images are overlaid to facilitate interpretation of the localization of the vitronectin targeted imaging in the body, relative to the distribution of the perfusion agent in the body.

50. (original) The method according to claim 1, for use in concurrent imaging sites of angiogenesis and organ perfusion.

51. (original) The method according to claim 1, for use in diagnosing and localizing sites of angiogenesis and perfusion abnormalities.

52. (original) The method according to claim 1, for use in concurrent detection and localization of sites of endothelial damage and perfusion abnormalities.

53. (original) The method according to claim 1, for use in the concurrent detection and localization of sites of vulnerable plaque and perfusion abnormalities.

54. (original) The method according to claim 1, wherein administering the vitronectin targeted imaging agent and a perfusion imaging agent is concurrent.

55. (original) The method according to claim 1, wherein administering the vitronectin targeted imaging agent and a perfusion imaging agent is sequential.

56. (original) The method according to claim 1, wherein the vitronectin targeted imaging agent and a perfusion imaging agent are administered in a synergistically effective amount.

57. (original) The method according to claim 1, wherein the gamma-emission energies of the vitronectin targeted imaging agent and the perfusion imaging agent are spectrally separable by pulse-height analysis.
58. (original) The method according to claim 1, wherein the difference in gamma emission spectral energies of the vitronectin antagonist diagnostic metallopharmaceutical and the perfusion imaging agent is >10Kev.
59. (original) The method of claim 1 wherein the perfusion imaging agent is a radiolabelled imaging agent, which is radiolabeled with Tc-99m or Tl-201.
60. (original) The method of claim 4 wherein the ultrasound perfusion agent is comprised of a gaseous microbubble or liquid emulsion.
61. (original) The method of claim 4 wherein the ultrasound perfusion agent is a perfluorocarbon gas.
62. (original) The method of claim 4 wherein the ultrasound perfusion agent is a perfluorocarbon liquid.
63. (original) The method of claim 4 wherein the MRI perfusion imaging agent is comprised of Gd(III), Dy(III), Fe(III), or Mn(II).
64. (Canceled).
65. (original) The method of claim 4 wherein the MRI perfusion imaging agent is selected from the group: trisodium (2(R)-((4, 4-diphenylcyclohexyl)(hydroxy)phosphoryloxymethyl) diethylenetriaminopentaacetato(6-))-gadolate(3-), gadopentetic acid, gadodiamide, and gadoteridol.

DOCKET NO.: BMS-2201 (PH-7201)
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PROCEDURE PURSUANT TO
37 CFR § 1.116**

66. (original) The method of claim 4 wherein the MRI perfusion imaging agent is the vitronectin receptor targeted imaging agent which is unbound to the vitronectin receptor.